Analgesia

Rates of Adverse Events of Long-Acting Opioids in a State Medicaid Program

Daniel M Hartung, Luke Middleton, Dean G Haxby, Michele Koder, Kathy L Ketchum, and Roger Chou

BACKGROUND: Despite widespread use and emerging safety concerns, data on the comparative safety and effectiveness of long-acting opioid (LAO) analgesics are weak.

OBJECTIVE: To compare rates of adverse events among patients newly prescribed an LAO.

METHODS: A retrospective observational cohort study using Medicaid administrative claims data was conducted examining time until first adverse outcome among patients with new prescriptions for methadone, extended-release (ER) oxycodone, ER morphine, or transdermal fentanyl. Adverse outcomes included emergency department (ED) encounters or hospitalizations for opioid-related adverse events, all-cause ED encounters or hospitalizations, death, and diagnoses for opioid-related adverse effects. Cox proportional hazards models were used to adjust for a variety of measured covariates overall and within subgroups of patients with and without cancer.

RESULTS: This study included 5684 subjects. Patients prescribed ER oxycodone were 35% less likely (adjusted hazard ratio [HR] 0.45; 95% CI 0.26 to 0.77) to experience an ED or hospitalization involving an opioid-related adverse event, 23% lower risk of hospitalization (adjusted HR 0.77; 95% CI 0.66 to 0.91), 41% lower risk of constipation (adjusted HR 0.59; 95% CI 0.35 to 1.00), and a 29% lower risk of death (adjusted HR 0.71; 95% CI 0.54 to 0.94) compared with those prescribed ER morphine. Among subjects with noncancer pain, fentanyl was associated with a higher risk of ED encounters (adjusted HR 1.27; 95% CI 1.02 to 1.59) and methadone was associated with a greater risk of overdose symptoms (adjusted HR 1.57; 95% CI 1.03 to 2.40) compared with ER morphine.

CONCLUSIONS: Our results support a modest safety advantage with ER oxycodone compared with ER morphine. Among subjects with noncancer pain, fentanyl and methadone were associated with an increased risk of an adverse event compared with ER morphine. Additional studies are needed to confirm our findings and further clarify risks associated with different LAOs.

KEY WORDS: adverse effects, opioid analgesics, pharmacoepidemiology.

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The role of long-acting opioid (LAO) analgesics for the treatment of chronic cancer and noncancer pain has expanded considerably in recent years. Drug utilization and distribution data indicate that the use of opioids has increased substantially in the last 20 years.[1-3] These trends are likely due to the increased recognition of chronic pain as an important and treatable phenomenon, as well as increased familiarity by prescribers about the clinical use of opioid analgesics.[4] While abuse and dependence remain a concern among prescribers, professional organizations have stressed the need to address untreated or undertreated chronic pain.[4]

LAOs, like other opioids, are associated with a number of well-known adverse effects such as respiratory and central nervous system depression, constipation, and physical dependence. Despite the proliferation of LAO use, evidence that compares the available products is either lacking or clinically equivocal. A systematic review found very few high-quality data comparing the effectiveness and safety of LAOs for the treatment of chronic noncancer pain.[5] One randomized trial included in that review found less constipation with transdermal fentanyl compared with extended-release (ER) morphine.[6] However, this study was deemed of poor quality because of a lack of blinding and previous exposure to morphine in most patients prior to study entry. Less constipation with transdermal fentanyl has also been reported in trials of patients with cancer, as well as in a claims-based observational study.[7,8]

The widespread use of opioid analgesics is also concerning given recent reports highlighting safety issues. Surveillance based on death certificate data from the National Center for Health Statistics suggests that opioid

Author information provided at the end of the text.

analgesics were associated with the largest increase in accidental poisonings between 1999 and 2002, marking the first time that legal drugs were cited in more accidental deaths than illicit drugs.[9] The Drug Abuse Warning Network, a public health surveillance database of drug-related emergency department (ED) visits and deaths, found that ED encounters mentioning prescription opioids increased 168% between 1994 and 2002 compared with 29% for alcohol, 39% for cocaine, and 48% for heroin.[10]

Anecdotal reports of increasing toxicity to specific opioids have also been publicized recently.

Methadone has experienced resurgence in use as an analgesic because of its low cost compared with the cost of other LAOs. Despite the absence of compelling data suggesting differences in the effectiveness and safety compared with other LAO preparations, many healthcare professionals have voiced concerns about the safety of methadone relative to other opioids.[11] An analysis of death certificates in Oregon found a fourfold increase in the number of methadone-related deaths from 1999 to 2002.[12] Further investigation revealed pain management to be the primary indication for methadone in a significant proportion of these subjects, suggesting nonillicit use. Similar observations have emerged in North Carolina, Maryland, and Utah.[9,12-14] Additionally, the Food and Drug Administration has issued a public health advisory on the increasing frequency of accidental overdoses with transdermal fentanyl.[15] Despite concerns and reports of adverse events, large-scale safety investigations are lacking.

Methods

The goal of this study was to evaluate the risk of serious adverse events among Oregon fee-for-service Medicaid recipients prescribed LAOs using a retrospective observational cohort methodology. Four cohorts were established based on the index prescription fill, defined as the first prescription claim during the study period, for one of the following LAOs: methadone (Dolophine and generics), ER oxycodone (Oxycontin and generics), ER morphine (MS Contin, Oramorph, Kadian, Avinza, and generics), and transdermal fentanyl (Duragesic and generics). Subjects were included if they had at least one prescription of at least 28 days' supply between January 1, 2000, and December 31, 2004, and at least 180 days of continuous Medicaid fee for service program eligibility prior to their first (index) fill. Continuous exposure was defined as successive LAO prescriptions at a maximum interval of 31 days from the last prescription's days' supply.

OUTCOMES AND COVARIATES

The primary outcome was the first administrative claim for an ED visit or hospitalization with a diagnostic code suggesting an opioid-related adverse event. Specifically, ED and hospitalizations with an ICD-9 diagnosis code for poisoning by opiates and related narcotics (9650x); alteration of consciousness (7800x); malaise, fatigue, or lethargy (7807x); respiratory failure (51881, 51882); or constipation (5640x) were identified. An ED encounter was identified by procedure and revenue center codes. Subjects with a Current Procedural Terminology code of 99281-99285 or 99288 or an ED revenue center code of 45x or 981 were considered to have had an ED encounter. Hospitalizations were identified using the Diagnosis-Related Group coding system. The rates of all-cause ED encounters and hospitalization, as well as any encounter for poisoning by opiates (9650x); symptoms of opioid-related adverse effects (alteration of consciousness [7800x]; malaise, fatigue, or lethargy [7807x]; or respiratory failure [51881, 51882]); and constipation (5640x) were compared between cohorts. To provide estimates of differences in the rate of all-cause mortality, data from the monthly vital statistics report provided by the Oregon Center for Health Statistics were evaluated.

Comparisons between cohorts were statistically adjusted for the following covariates: age, race, sex, long-term care residence, number of unique prescribers, disease severity, concomitant prescription claims for drugs with known pharmacodynamic interactions with LAOs, the type of presumed pain diagnosis, and a history of opioid dependence, abuse, or enrollment in a substance abuse treatment program. Pain diagnoses were identified using ICD-9 codes from medical encounter claims processed one year before and after a subject's cohort entry date and included osteoarthritis (715x), back pain ([dorsopathies] 720x–724x), peripheral nervous system disorders (350x–359x), fibromyalgia (7291), and neoplasm (140x–239x). The prevalence of opioid dependence (3040x, 3047, 3049), abuse (3055), or enrollment in a state-monitored substance abuse program was also quantified and adjusted for.

The adapted Charlson Comorbidity Index was used as the disease severity measure. The Charlson Index was originally developed as a predictor of mortality in medical subjects as a function of other comorbid conditions and is frequently used in observational studies as an overall indicator of health status.[16] It has subsequently been adapted and validated for use with administrative claims.[17] Diagnosis codes during the 5 years of the study period for each subject were used to calculate each subject's Charlson Index.

To evaluate the impact of concomitant medications, the number of unique, concomitant, potentially interacting drugs prescribed during the subject's exposure period were counted. We defined potentially interacting drugs as benzodiazepines, sedative hypnotics (eg, barbiturates, zolpidem), muscle relaxants (eg, carisoprodol, cyclobenzaprine), and short-acting opioids (eg, oxycodone, hydrocodone). For each cohort, the average daily dose of long- and short-acting opioids was calculated and converted to a morphine-equivalent daily dose over the exposure period. Dai-

ly doses of 4 mg of methadone and 20 mg of oxycodone were considered equianalgesic with 30 mg daily of oral morphine sulfate.[18] The daily dose of fentanyl was converted based on data suggesting a conversion using a ratio of 100 mg daily morphine equianalgesic to 1 mg daily transdermal fentanyl.[19] Finally, we quantified whether a different LAO was started subsequent to the end of the patients' original LAO exposure (LAO change).

In addition to evaluating adverse outcomes overall, we also examined the occurrence of these outcomes in 2 mutually exclusive subgroups: subjects with a diagnosis of cancer and those without cancer who had a diagnosis of osteoarthritis, fibromyalgia, back pain, or neuropathy.

STATISTICAL ANALYSIS

Cox proportional hazards models were used to evaluate the relationship between exposure to one of the studied LAOs and occurrence of one of the prespecified outcomes. Subjects in the ER morphine cohort were used as the reference cohort because morphine is typically considered to be the gold standard opioid. Subjects were removed from further follow-up if they (1) stopped therapy as defined above, (2) reached the end of the study period, or (3) had a fill for another LAO. For each model, covariates were evaluated using forward stepwise procedures, with p values for entry of 0.25 and 0.05 to remain in the model. Covariates and main effect indicator variables (group allocation dummy variables) in the final model were considered statistically significant with a p value less than or equal to 0.05. Results are presented with p values and 95% confidence intervals. Demographic data were evaluated using a χ^2 test of proportion or one-way analysis of variance for categorical and continuous data, respectively. Fisher's exact test was used in place of χ^2 if cell sizes were small (<5 observations/cell). SAS version 9.1 was used for all analyses. This study was approved by the Oregon State University Institutional Review Board.

Results

Over the study period, 5684 unique subjects had an index prescription for an LAO with a minimum 28 days' supply. The largest cohort was prescribed oxycodone ER; the smallest was prescribed methadone. Multiple statistically significant differences among the cohorts' characteristics were noted (Table 1). The transdermal fentanyl cohort was older and had a significantly higher proportion of women and subjects residing in a long-term care facility. The methadone cohort was younger, was on the greatest morphine-equivalent dose, and had the highest prevalence of diagnoses for back pain, fibromyalgia, osteoarthritis, and diagnoses of substance abuse or dependence. The morphine ER cohort had a higher prevalence of a malignancy. Subjects in the oxycodone ER cohort were most likely to have a prescription for a different LAO after their follow-up ended.

Table 2 shows the absolute incidence of the various outcomes, as well as adjusted hazard ratios (HRs) generated from multivariate Cox proportional hazards models. For the primary outcome of time to first ED or hospitalization for opioid-related adverse events, subjects in the oxycodone ER cohort were 35% less likely to have an event compared with the morphine ER cohort. Time to first event in the trans-

Table 1. Cohort Demographics

Characteristic	Transdermal Fentanyl	Methadone	ER Oxycodone	ER Morphine	p Value
N = 5684	1546	974	1866	1298	
Age, y (mean ± SD)	70.6 ± 18.1	51.1 ± 15.4	57.4 ± 17.9	58.5 ± 17.0	<0.001
Prescribers, n (mean ± SD)	2.5 ± 1.9	2.6 ± 2.4	2.6 ± 1.9	2.6 ± 2.1	0.256
Interacting drug, n (mean ± SD)	1.5 ± 1.2	1.4 ± 1.3	1.7 ± 1.3	1.5 ± 1.2	<0.001
Charlson Comorbidity Index (mean ± SD)	1.0 ± 1.7	0.9 ± 1.5	1.2 ± 1.9	1.4 ± 2.1	<0.001
Equivalent dose/day (mean ± SD)	96.0 ± 42.5	246.6 ± 310.9	66.7 ± 79.4	74.0 ± 78.5	<0.001
Short-acting opioid equivalent dose/day (mean ± SD)	4.3 ± 14.8	4.5 ± 12.2	5.8 ± 15.7	3.1 ± 7.3	<0.001
Switched LAO after follow-up, n (%)	234 (15.1)	170 (17.5)	572 (30.7)	242 (18.6)	<0.001
Female, n (%)	1144 (74.0)	615 (63.1)	1208 (64.7)	848 (65.3)	<0.001
Non-white, n (%)	95 (6.1)	102 (10.5)	143 (7.7)	125 (9.6)	<0.001
Long-term care residence, n (%)	439 (28.4)	40 (4.1)	185 (9.9)	160 (12.3)	<0.001
Non-English speaker, n (%)	25 (1.6)	15 (1.5)	21 (1.1)	25 (1.9)	0.323
Cancer, n (%)	307 (19.9)	178 (18.3)	471 (25.2)	339 (26.1)	<0.001
Osteoarthritis, n (%)	212 (13.7)	220 (22.6)	361 (19.3)	234 (18.0)	<0.001
Fibromyalgia, n (%)	73 (4.7)	176 (18.1)	185 (9.9)	118 (9.1)	<0.001
Back pain, n (%)	271 (17.5)	407 (41.8)	654 (35.0)	355 (27.3)	<0.001
Neuropathic pain, n (%)	112 (7.2)	163 (16.7)	148 (7.9)	244 (18.8)	<0.0001
Substance abuse treatment center, n (%)	19 (1.2)	86 (8.8)	68 (3.6)	46 (3.5)	<0.0001
Substance abuse, n (%)	2 (0.1)	9 (0.9)	2 (0.1)	3 (0.2)	<0.001
Substance dependence, n (%)	15 (1.0)	91 (9.3)	47 (2.5)	17 (1.3)	<0.001

ER = extended-release; LAO = long-acting opioid.

dermal fentanyl and methadone cohorts did not significantly differ from the time in the morphine ER cohort.

Subjects in the oxycodone ER cohort were also 29% less likely to die compared with subjects in the morphine ER cohort. There was a trend toward improved survival among the methadone and fentanyl cohorts, although neither difference reached statistical significance.

There were no significant differences between cohorts in the risk of any ED encounter. However, subjects prescribed methadone or oxycodone ER were significantly less likely to be hospitalized compared with morphine ER by 18% and 23%, respectively. There were no significant differences between cohorts in the risk of symptoms of overdose or the risk of being diagnosed with opioid poisoning. Subjects prescribed oxycodone ER were 41% less likely to develop a diagnosis of constipation compared with those prescribed morphine ER.

The demographics of the cancer and noncancer pain subgroups are shown in Tables 3 and 4. A total of 1295 subjects were identified with a cancer diagnosis and 2027 had a noncancer pain diagnosis. The subgroup of subjects with a cancer diagnosis generally received higher equiva-

Table 2. Unadjusted Incidence Rate and Adjusted Cox Proportional Hazards Model

Parameter	Events, n	Person Years	Incidence/100 Person Years	Adjusted HR	95% CI	p Value
ED encounter or hospitalization for opioid-related adverse event[a,b]						
methadone	17	473	3.6	0.71	0.39 to 1.29	0.259
oxycodone	22	909	2.4	0.45	0.26 to 0.77	0.004
fentanyl	28	779	3.6	0.73	0.44 to 1.23	0.241
morphine (referent)	31	541	5.7			
Mortality[c]						
methadone	29	476	6.1	0.71	0.46 to 1.08	0.105
oxycodone	99	912	10.9	0.71	0.54 to 0.94	0.018
fentanyl	287	785	36.5	0.80	0.63 to 1.02	0.071
morphine (referent)	107	546	19.6			
ED encounters[d]						
methadone	385	396	97.3	1.01	0.87 to 1.18	0.877
oxycodone	685	768	89.2	0.92	0.81 to 1.03	0.156
fentanyl	501	692	72.4	1.03	0.90 to 1.18	0.640
morphine (referent)	464	476	97.5			
Hospitalizations[e]						
methadone	178	404	44.0	0.82	0.68 to 0.99	0.043
oxycodone	354	786	45.0	0.77	0.66 to 0.91	0.002
fentanyl	297	697	42.6	0.93	0.79 to 1.10	0.392
morphine (referent)	276	460	60.0			
Opioid poisoning[f]						
methadone	6	475	1.3	3.22	0.60 to 17.25	0.171
oxycodone	3	910	0.3	0.87	0.14 to 5.25	0.879
fentanyl	1	789	0.1	0.46	0.04 to 5.12	0.528
morphine (referent)	2	545	0.4			
Overdose symptoms[g,h]						
methadone	113	442	25.6	1.11	0.85 to 1.44	0.455
oxycodone	167	865	19.3	0.89	0.70 to 1.13	0.324
fentanyl	135	752	17.9	0.97	0.75 to 1.24	0.778
morphine (referent)	120	516	23.3			
Constipation[i]						
methadone	22	470	4.7	0.85	0.49 to 1.48	0.559
oxycodone	28	900	3.1	0.59	0.35 to 1.00	0.049
fentanyl	27	778	3.5	0.78	0.46 to 1.33	0.361
morphine (referent)	29	535	5.4			

ED = emergency department; LAO = long-acting opioid.

[a]Adjusted for Charlson Index.

[b]Constipation, alteration of consciousness, malaise, fatigue, lethargy, respiratory failure, opioid poisoning.

[c]Adjusted for long-term care, sex, age, osteoarthritis, neuropathies, back pain, Charlson Index, number of prescribers, number of medications, short-acting opioid dose, LAO change.

[d]Adjusted for long-term care, sex, age, cancer, osteoarthritis, back pain, Charlson Index, number of prescribers, substance dependence, treatment center, dose, short-acting opioid dose, LAO change.

[e]Adjusted for long-term care, race, cancer, osteoarthritis, Charlson Index, substance abuse, short-acting opioid dose, LAO change.

[f]Adjusted for Charlson Index, number of medications, substance dependence.

[g]Adjusted for race, fibromyalgia, back pain, Charlson Index, number of medications, substance abuse, and short-acting opioid dose.

[h]Alteration of consciousness, malaise, fatigue, lethargy, respiratory failure.

[i]Adjusted for long-term care.

lent doses of long- and short-acting opioids and were more likely to reside in a long-term care facility compared with the total population. The subgroup with a noncancer pain diagnosis was generally younger and also was less likely to reside in long-term care facility. Subjects in the cancer cohort had a higher average Charlson Comorbidity Index, due in part to the higher weight given to a cancer diagnosis.

A summary of outcomes measured in these 2 subgroups is shown in Table 5. Subjects with a diagnosis of cancer in the oxycodone ER cohort had a significantly lower risk of hospitalization than those prescribed morphine ER. Overall, however, the HR observed for subjects with a cancer diagnosis were similar to estimates for the total population. Among subjects with noncancer pain diagnoses, the risk of

Table 3. Demographics of Subjects with Cancer

Parameter	Transdermal Fentanyl	Methadone	ER Oxycodone	ER Morphine	p Value
N = 1295	307	178	339	471	
Age, y (mean ± SD)	64.6 ± 16.2	52.8 ± 13.5	57.5 ± 14.9	57.0 ± 15.0	<0.001
Prescribers, n (mean ± SD)	2.9 ± 2.3	3.4 ± 3.2	2.9 ± 2.5	2.8 ± 2.1	0.037
Interacting drugs, n (mean ± SD)	1.6 ± 1.4	1.6 ± 1.4	1.7 ± 1.2	1.8 ± 1.4	0.335
Charlson Comorbidity Index (mean ± SD)	2.7 ± 2.5	1.9 ± 2.4	3.3 ± 2.8	2.7 ± 2.6	<0.001
Equivalent dose/day (mean ± SD)	102.76 ± 90.0	248.43 ± 153.5	75.47 ± 58.7	85.1 ± 60.0	<0.001
Short-acting opioid equivalent dose/day (mean ± SD)	5.7 ± 11.6	5.2 ± 18.4	6.5 ± 12.6	4.8 ± 9.8	0.262
Switched LAO after follow-up, n (%)	55 (17.9)	39 (21.9)	143 (30.4)	68 (20.1)	<0.001
Female, n (%)	207 (67.4)	125 (70.2)	207 (61.1)	304 (64.5)	0.150
Non-white, n (%)	27 (8.8)	19 (10.7)	29 (8.6)	41 (8.7)	0.860
Long-term care resident, n (%)	38 (12.4)	8 (4.5)	24 (7.1)	27 (5.7)	0.002
Non-English speaker, n (%)	9 (2.9)	4 (2.2)	13 (3.8)	8 (1.7)	0.2916
Osteoarthritis, n (%)	65 (21.2)	50 (28.1)	57 (16.8)	92 (19.5)	0.023
Fibromyalgia, n (%)	23 (7.5)	38 (21.3)	30 (8.8)	43 (9.1)	<0.0001
Back pain, n (%)	78 (25.4)	76 (42.7)	91 (26.8)	175 (37.2)	<0.0001
Neuropathic pain, n (%)	32 (10.4)	39 (21.9)	39 (11.5)	67 (14.2)	0.002
Substance abuse treatment center, n (%)	5 (1.6)	13 (7.3)	12 (3.5)	21 (4.5)	0.017
Substance abuse, n (%)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.2)	0.809
Substance dependence, n (%)	4 (1.3)	16 (9.0)	3 (0.9)	13 (2.8)	<0.0001

ER = extended-release; LAO = long-acting opioid.

Table 4. Demographics of Subjects with Other Pain-Related Conditions[a]

Parameter	Transdermal Fentanyl	Methadone	ER Oxycodone	ER Morphine	p Value
N = 2027	338	508	447	734	
Age, y (mean ± SD)	62.5 ± 18.9	48.9 ± 13.2	53.7 ± 15.4	52.5 ± 16.0	<0.001
Prescribers, n (mean ± SD)	2.7 ± 2.2	2.7 ± 2.2	2.7 ± 2.2	2.7 ± 2.1	0.983
Interacting drugs, n (mean ± SD)	1.67 ± 1.4	1.56 ± 1.3	1.74 ± 1.3	1.94 ± 1.5	<0.001
Charlson Comorbidity Index (mean ± SD)	0.86 ± 1.2	0.64 ± 1.1	0.83 ± 1.3	0.8 ± 1.2	0.020
Equivalent dose/day (mean ± SD)	98.4 ± 44.6	236.6 ± 247.5	67.0 ± 66.3	77.2 ± 72.2	<0.001
Short-acting opioid equivalent dose/day (mean ± SD)	4 ± 8.2	8.23 ± 9.1	5.99 ± 21.9	2.55 ± 6.0	<0.001
Switched LAO after follow-up, n (%)	90 (26.6)	102 (20.1)	258 (35.1)	100 (22.4)	<0.001
Female, n (%)	255 (75.4)	327 (64.4)	299 (66.9)	473 (64.4)	0.002
Non-white, n (%)	21 (6.2)	51 (10.0)	52 (11.6)	57 (7.8)	0.028
Long-term care resident, n (%)	65 (19.2)	8 (1.6)	34 (7.6)	37 (5.0)	<0.001
Non-English speaker, n (%)	6 (1.8)	7 (1.4)	8 (1.8)	4 (0.5)	0.180
Osteoarthritis, n (%)	147 (43.5)	170 (33.5)	177 (39.6)	269 (36.6)	0.021
Fibromyalgia, n (%)	50 (14.8)	138 (27.2)	88 (19.7)	142 (19.3)	<0.001
Back pain, n (%)	193 (57.1)	331 (65.2)	264 (59.1)	479 (65.3)	0.016
Neuropathic pain, n (%)	80 (23.7)	124 (24.4)	109 (24.4)	177 (24.1)	0.995
Substance abuse treatment center, n (%)	12 (3.6)	49 (9.6)	20 (4.5)	30 (4.1)	<0.001
Substance abuse, n (%)	1 (0.3)	6 (1.2)	2 (0.4)	0 (0.0)	0.010
Substance dependence, n (%)	9 (2.7)	43 (8.5)	11 (2.5)	21 (2.9)	<0.001

ER = extended-release; LAO = long-acting opioid.
[a]Osteoarthritis, fibromyalgia, back pain, or neuropathic pain.

several adverse outcomes differed qualitatively from the risk for the cancer cohort and the overall population. The transdermal fentanyl cohort had a statistically significant increase in risk for ED encounter compared with the morphine ER cohort. The risk of experiencing a symptom of overdose was 57% higher in the methadone group compared with the morphine ER cohort.

Discussion

In this observational cohort study, subjects prescribed oxycodone ER were significantly less likely than subjects prescribed morphine ER to experience several adverse outcomes including ED or hospital encounter for opioid-related adverse events, all-cause hospitalization, constipation, and death. Absolute risk reductions can be estimated by subtracting the incidence rates for a given outcome for each cohort from the reference cohort. In absolute and unadjusted terms, subjects prescribed oxycodone ER experienced about 3.3 ED encounters or hospitalizations for opioid-related adverse events, 8.4 ED encounters, 15.0 hospitalizations, and 8.7 deaths per 100 person years less than those prescribed morphine ER. Patients prescribed methadone or transdermal fentanyl were no more likely than those prescribed morphine ER to experience one of the adverse outcomes studied, and in fact, those prescribed methadone were less likely to experience a hospitalization.

Subgroup analyses of subjects with a cancer diagnosis or a noncancer pain-related diagnosis were generally similar to the overall analysis. Notable exceptions were among noncancer subjects who experienced an increased risk of any ED visit if they were prescribed transdermal fentanyl and an increased risk for having a diagnosis for an opioid-related overdose symptom if they were prescribed methadone.

Table 5. Adjusted Cox Proportional Hazard Models Among Patients with Specific Pain Diagnoses

	Cancer			Noncancer		
Parameter	**HR**	**95% CI**	**p Value**	**HR**	**95% CI**	**p Value**
ED/hospitalization[a]						
methadone	0.24	0.05 to 1.13	0.071	0.70	0.29 to 1.69	0.426
oxycodone	0.68	0.27 to 1.72	0.411	0.52	0.22 to 1.23	0.138
fentanyl	1.08	0.43 to 2.74	0.870	1.42	0.63 to 3.21	0.404
morphine (referent)						
Mortality						
methadone	0.48	0.18 to 1.23	0.127	0.78	0.29 to 2.13	0.628
oxycodone	0.74	0.46 to 1.21	0.226	0.98	0.45 to 2.14	0.961
fentanyl	0.93	0.58 to 1.49	0.768	0.89	0.43 to 1.84	0.753
morphine (referent)						
ED encounters						
methadone	0.79	0.61 to 1.04	0.089	1.13	0.91 to 1.41	0.286
oxycodone	0.88	0.71 to 1.08	0.215	0.91	0.76 to 1.10	0.327
fentanyl	0.98	0.78 to 1.22	0.837	1.27	1.02 to 1.59	0.034
morphine (referent)						
Hospitalizations						
methadone	0.85	0.61 to 1.17	0.313	1.09	0.78 to 1.52	0.630
oxycodone	0.73	0.56 to 0.94	0.014	0.87	0.67 to 1.14	0.327
fentanyl	1.06	0.82 to 1.39	0.644	1.16	0.85 to 1.59	0.356
morphine (referent)						
Opioid poisoning						
methadone	2.20	0.13 to 38.76	0.590	2.41	0.26 to 22.59	0.441
oxycodone	0.41	0.02 to 8.30	0.560	1.16	0.11 to 12.83	0.903
fentanyl						
morphine (referent)						
Overdose symptoms[b]						
methadone	1.04	0.65 to 1.66	0.881	1.57	1.03 to 2.40	0.037
oxycodone	0.77	0.52 to 1.16	0.215	1.07	0.74 to 1.53	0.731
fentanyl	1.05	0.69 to 1.60	0.826	1.10	0.72 to 1.68	0.672
morphine (referent)						
Constipation						
methadone	0.80	0.27 to 2.40	0.693	0.66	0.29 to 1.53	0.334
oxycodone	0.52	0.19 to 1.39	0.192	0.72	0.34 to 1.55	0.403
fentanyl	1.24	0.51 to 2.99	0.636	0.95	0.40 to 2.25	0.902
morphine (referent)						

ED = emergency department.
[a]Constipation, alteration of consciousness, malaise, fatigue, lethargy, respiratory failure, opioid poisoning.
[b]Alteration of consciousness, malaise, fatigue, lethargy, respiratory failure.

Limitations

Our study has several limitations. First, we relied on encounter claims from administrative databases, which may have led to misclassification errors, as the accuracy of many of the diagnostic codes that we used have not been validated. However, a review found that specificity of several commonly used diagnostic codes is actually quite high (>95% for many diseases).[20] High specificity of diagnostic coding, regardless of sensitivity, generally results in random misclassification and unbiased estimates of risk.[21] Some outcomes measured for this study (any ED or hospitalization) were relatively nonspecific surrogates for potential adverse events. It is very likely that many of the events observed were not related to use of the prescribed LAO.

Secondly, this was an observational study, and subjects were not randomly assigned to treatment. As such, substantial differences in patient characteristics were expected and observed. Although differences in measured covariates were statistically adjusted for in the Cox proportional hazard models, unmeasured confounding factors may still be present. Because we used an administrative claim dataset, clinical data that could provide additional or more accurate information on potential confounders (eg, physical characteristics, dietary intake, alcohol use, or direct measures of illicit drug use) were not available. The potential effects of residual confounding are important to consider in this study because observed HRs were generally small and large differences between cohorts in population characteristics were observed.[22,23]

Another limitation is the assumption that dispensed prescriptions were actually consumed as indicated on the pharmacy claim. In general, pharmacy claims have been demonstrated to be an accurate measure of prescription drug consumption.[24] However, inappropriate use and diversion of opioid analgesics is a concern that is difficult to quantify. We attempted to control characteristics associated with opioid abuse by quantifying whether the subject had a history of opioid abuse, or dependence or was enrolled in a substance abuse treatment program.

Finally, this analysis was performed using Medicaid data. Medicaid is primarily a healthcare program for low-income and vulnerable populations (ie, groups that may be disproportionally affected by policy, economic conditions, access problems); therefore, the findings may not be applicable to other populations of LAO users.

Conclusions

This retrospective observational cohort study suggests that oxycodone ER may have a moderate safety advantage over morphine ER. Subjects prescribed oxycodone ER experienced significantly lower risk of the combined outcome of an ED or hospitalization for opioid-related adverse effects, as well as for the individual outcomes all-cause death, hospitalization, and constipation compared with those prescribed morphine ER. Subjects prescribed methadone were less likely to be hospitalized than those prescribed morphine ER. Among patients with noncancer pain, transdermal fentanyl and methadone were associated with more adverse outcomes than ER morphine.

While the results suggest that different LAOs may vary on important adverse events, they should be interpreted with caution because the magnitude of differences was small, there were large differences between studied cohorts, and some outcomes were not specific for opioid-associated toxicity. Our findings should be confirmed in other populations and settings, and inferences about comparative safety of LAOs would be strengthened by well-designed prospective cohort studies that are able to supplement administrative databases with additional clinical data on opioid exposures, covariates, and opioid-related adverse events.

Daniel M Hartung PharmD MPH, Assistant Professor, Pharmacy Practice, College of Pharmacy, Oregon State University, Oregon Health & Science University Campus, Portland, OR

Luke Middleton BS, Data Analyst, College of Pharmacy, Oregon State University, Oregon Health & Science University Campus

Dean G Haxby PharmD, Associate Professor of Pharmacy Practice, College of Pharmacy, Oregon State University, Oregon Health & Science University Campus

Michele Koder PharmD, Clinical Pharmacy Specialist, College of Pharmacy, Oregon State University, Oregon Health & Science University Campus

Kathy L Ketchum BS Pharm MPA:HA, Coordinator for Medicaid-Related Programs, College of Pharmacy, Oregon State University, Oregon Health & Science University Campus

Roger Chou MD, Assistant Professor of Medicine and Medical Informatics & Clinical Epidemiology, Oregon Health and Science University, Oregon Evidence-Based Practice Center, Portland

Reprints: Dr. Hartung, College of Pharmacy, Oregon State University, Oregon Health & Science University Campus, 3303 SW Bond Ave., Mail Code CH12C Portland, OR 97239, fax 503/494-1082, hartungd@ohsu.edu

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References

1. Novak S, Nemeth WC, Lawson KA. Trends in medical use and abuse of sustained-release opioid analgesics: a revisit. Pain Med 2004;5:59-65.
2. Joranson DE, Ryan KM, Gilson AM, Dahl JL. Trends in medical use and abuse of opioid analgesics. JAMA 2000;283:1710-4.
3. Zerzan JT, Morden NE, Soumerai S, et al. Trends and geographic variation of opiate medication use in state Medicaid fee-for-service programs, 1996 to 2002. Med Care 2006;44:1005-10.
4. The use of opioids for the treatment of chronic pain. A consensus statement from the American Academy of Pain Medicine and the American Pain Society. Clin J Pain 1997;13:6-8.
5. Chou R, Clark E, Helfand M. Comparative efficacy and safety of long-acting oral opioids for chronic non-cancer pain: a systematic review. Pain Symptom Manage 2003;26:1026-48.
6. Allan L, Hays H, Jensen NH, et al. Randomised crossover trial of transdermal fentanyl and sustained release oral morphine for treating chronic non-cancer pain. BMJ 2001;322:1154-8.
7. Staats PS, Markowitz J, Schein J. Incidence of constipation associated with long-acting opioid therapy: a comparative study. South Med J 2004; 27:129-34.

8. Haazen L, Noorduin H, Megens A, Meert T. The constipation-inducing potential of morphine and transdermal fentanyl. Eur J Pain 1999;3:9-15.
9. Paulozzi LJ, Budnitz DS, Xi Y. Increasing deaths from opioid analgesics in the United States. Pharmacoepidemiol Drug Saf 2006;15:618-27.
10. Trends in drug-related emergency department visits, 1994–2002 at a glance. Rockville, MD: US Department of Health & Human Services; Substance Abuse and Mental Health Services Administration, 2003. www.dawninfo.samhsa.gov/old_dawn/pubs_94_02/shortreports/files/DAWN_EDvisits_glance.pdf (accessed 2007 Mar 27).
11. Belluck P. Methadone, once the way out, suddenly grows as a killer drug. New York Times 2003;Feb 9. http://query.nytimes.com/gst/fullpage.html?sec=health&res=9A04E3DE103BF93AA35751C0A9659C8B63 (accessed 2007 May 2).
12. Methadone deaths (and distribution) on the rise. CD Summary 2003;52. www.oregon.gov/DHS/ph/cdsummary/2003/ohd5214.pdf (accessed 2007 Mar 27).
13. Ballesteros MF, Budnitz DS, Sanford CP, Gilchrist J, Agyekum GA, Butts J. Increase in deaths due to methadone in North Carolina (letter). JAMA 2003;290:40.
14. Maryland Drug Early Warning System. What is behind the rise in methadone deaths in Maryland? Center for Substance Abuse Research University of Maryland. May 2004. www.cesar.umd.edu/cesar/pubs/20040501.pdf (accessed 2007 May 2).
15. FDA public health advisory: safety warnings regarding use of fentanyl transdermal (skin) patches. Food and Drug Administration, 2005. www.fda.gov/cder/drug/advisory/fentanyl.htm (accessed 2007 Mar 27).
16. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373-83.
17. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol 1992;45:613-9.
18. Labby D, Koder M, Amann T. Opioids and chronic non-malignant pain: a clinician's handbook. Portland, OR: CareOregon, 2003. www.careoregon.org/provider/documents/Opioids.pdf (accessed 2007 Mar 27).
19. Donner B, Zenz M, Tryba M, Strumpf M. Direct conversion from oral morphine to transdermal fentanyl: a multicenter study in patients with cancer pain. Pain 1996;64:527-34.
20. Wilchesky M, Tamblyn RM, Huang A. Validation of diagnostic codes within medical services claims. J Clin Epidemiol 2004;57:131-41.
21. Schneeweiss S, Avorn J. A review of uses of health care utilization databases for epidemiologic research on therapeutics. J Clin Epidemiol 2005;58:323-37.
22. Flanders WD, Khoury MJ. Indirect assessment of confounding: graphic description and limits on effect of adjusting for covariates. Epidemiology 1990;1:239-46.
23. Winkelstein W Jr, Shillitoe EJ, Brand R, Johnson KK. Further comments on cancer of the uterine cervix, smoking, and herpesvirus infection. Am J Epidemiol 1984;119(1):1-8.
24. Lau HS, de Boer A, Beuning KS, Porsius A. Validation of pharmacy records in drug exposure assessment. J Clin Epidemiol 1997;50:619-25.

EXTRACTO

TRASFONDO: A pesar de su uso generalizado y de preocupaciones emergentes sobre seguridad, la información sobre la seguridad, y efectividad comparable de los opiáceos de acción prolongada es débil.

OBJETIVOS: La meta de este estudio era comparar las tasas de eventos adversos entre pacientes a los que se les recetó recientemente opiáceos de acción prolongada.

MÉTODOS: Se condujo un estudio de observación retrospectivo de cohorte con datos de reclamaciones administrativas a Medicaid y se examinó el tiempo que transcurrió hasta que se produjo el primer resultado adverso entre pacientes con recetas nuevas de metadona, oxicodona de liberación extendida, morfina de liberación extendida, o fentanil transdérmico. Los resultados adversos incluyeron visitas al departamento de urgencias u hospitalizaciones relacionadas con eventos adversos con opiáceos, visitas al departamento de urgencias u hospitalizaciones por todas las causas, muerte y diagnósticos por efectos adversos relacionados con opiáceos.

RESULTADOS: Este estudio incluyó 5684 sujetos individuales. Los pacientes a los que se les recetó oxicodona de liberación extendida tuvieron 35% menor probabilidad (tasa de riesgo ajustada 0.45; 95% IC 0.26 y 0.77) de experimentar una visita al departamento de urgencias u hospitalización que involucrara un evento adverso relacionado con opiáceos, 23% menos riesgo de hospitalización (tasa de riesgo ajustada 0.77; IC 0.66 y 0.91), 41% menor riesgo de estreñimiento (tasa de riesgo ajustada 0.59; 95% IC 0.35 y 0.998) y 29% menor riesgo de muerte (tasa de riesgo ajustada 0.71; 95% IC 0.54 y 0.94) comparado con aquellos a quienes se les recetó morfina de liberación extendida. Entre los sujetos con dolor no causado por cáncer, recetar fentanil y metadona fue asociado con más altos riesgos de visitas al departamento de urgencias (tasa de riesgo ajustada 1.27; 95% IC 1.02 y 1.59) y síntomas de sobredosis (tasa de riesgo ajustada 1.57; 95% IC 1.03 y 2.40) comparado con morfina de liberación extendida.

CONCLUSIONES: Nuestros resultados apoyan una ventaja modesta en seguridad con oxicodona de liberación extendida, comparada con morfina de liberación extendida. Entre sujetos con dolor no causado por cáncer, fentanil y metadona fueron asociados con un riesgo incrementado de sufrir un evento adverso, comparado con morfina de liberación extendida. Se necesitan estudios adicionales para confirmar nuestros hallazgos y clarificar más los riesgos asociados con los diferentes opiáceos de acción prolongada.

Ana E Vélez

RÉSUMÉ

INTRODUCTION: En dépit de l'utilisation répandue et des inquiétudes quant à l'innocuité des opiacés à longue durée d'action (OLA), il n'existe que très peu de données sur leur efficacité et leur sécurité d'utilisation.

OBJECTIF: Comparer la fréquence d'effets indésirables des OLA chez des néo-utilisateurs.

DEVIS EXPÉRIMENTAL: La banque de réclamations de Medicaid a été utilisée pour évaluer la fréquence d'effets indésirables secondaire à l'administration de novo de méthadone, d'oxycodone à libération prolongée (LP), de morphine à LP, ou de fentanyl par voie trans-cutanée. Les effets indésirables comptabilisés ont été définis de la façon suivante: les visites à l'urgence ou les hospitalisations pour effet indésirable relié aux opiacés, les visites à l'urgence ou les hospitalisations toutes causes confondues, les décès, et les diagnostics d'effets indésirables reliés aux opiacés. Un modèle de régression de Cox a été utilisé pour ajuster une série de covariables. Les données ont été analysées pour toute la cohorte ainsi que pour les patients avec ou sans diagnostic de cancer.

RÉSULTATS: Cette étude inclue 5684 sujets. Les patients recevant de l'oxycodone LP avaient 35% moins de risque (ratio de risque ajusté [RR] 0.45; 95% IC 0.26 à 0.77) d'avoir à aller à l'urgence ou d'être hospitalisé pour un effet indésirable relié aux opiacés. Le risque de visite à l'urgence ou d'hospitalisation toute cause confondue était de 23% moins élevé (RR ajusté 0.77; 95% IC 0.66 à 0.91) alors que le risque de constipation était 41% plus faible (RR ajusté 0.59; 95% IC 0.35 à 0.998). De plus, ces patients ont montré un risque de décès de 29% inférieur (RR ajusté 0.71; 95% IC 0.54 à 0.94) à ceux ayant reçu de la morphine LP. Chez les patients ayant une douleur non reliée au cancer, le fentanyl et la méthadone étaient associés à un risque plus élevé de visites à l'urgence (RR ajusté 1.27; 95% IC 1.02 à 1.59) et de symptômes reliés à une surdose (RR ajusté 1.57; 95% IC 1.03 à 2.40) comparé à ceux ayant reçu de la morphine LP.

CONCLUSIONS: Nos résultats suggèrent un avantage modeste de l'oxycodone LP au niveau de l'innocuité en comparaison à la morphine LP. Chez les patients souffrant de douleurs non reliées au cancer, le fentanyl, et la méthadone sont associés à un risque plus élevé d'effets indésirables que la morphine LP. Des études additionnelles seront nécessaires pour confirmer nos résultats et clarifier les risques associés aux différents ALO.

Suzanne Laplante